review

Darwin, medicine and cancer

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'Nothing in biology makes sense except in the light of evolution'! So said Theodore Dobzhansky. It is extraordinary how little Darwinism and post-Darwinian evolutionary science has penetrated medicine despite the fact that all biology is built upon its foundations. Randy Nesse, one of the fathers of Darwinian medicine, recently observed that doctors 'know the facts but not the origins'. Clearly, then, in this auspicious year—200 years since Charles Darwin's birth and 150 years since the first edition of the *Origin of Species*—it is time to reconsider Darwin's legacy to medicine and to invite evolution back into the biomedical fold. Here, we consider the legacy of Darwin and the contribution of the other great evolutionists such as Ernst Mayr to cancer and medicine.

Key words: Darwin, evolution, Tinbergen, Mayr, Dobzhansky

Darwin: man of medicine

There has been little commentary on the relative importance that medicine played in the life of Charles Darwin. Of the facts we know this; Dr Robert Waring Darwin (1766–1848), his father, was a GP with an extensive practice in the Shrewsbury area and Erasmus Darwin (1731–1802), physician, poet, botanist and Charles's grandfather, was certainly influential (although later rejected by Darwin as being speculative and ineffectual) with his writings on evolution and sexual life [1]. WFA Ainsworth (1807–1896) as well as being a surgeon, also wrote extensively on geology, and Darwin was particularly taken with Sir Charles Bell's (1774–1842, anatomist and surgeon) research on human nervous system, which influenced his work on the expression of emotions. Charles Darwin's only and elder brother studied medicine at Edinburgh, qualifying in 1826, but never practised instead moved into the life of a London bachelor.

Perhaps fortunately for history, when it came time for Darwin to be dispatched to Edinburgh to study medicine in the winter of 1825, he took an almost instantaneous dislike to his studies, according to his autobiographical recollections [2]. He found most of the subjects and lecturers dull (Dr Duncan's *Materia Medica*) or disgusting (any and all surgery and dissection), despite taking obvious pride in his father's observation that he would make a fine doctor. But there is no doubt, from even the most cursory digest of his autobiography that Charles Darwin's interest in the natural sciences was further stimulated and developed by discourses with friends such as Ainsworth, Coldstream, Hardie, Grant and others. Medical studies at Edinburgh also provided a springboard for

Darwin to engage with like-minded senior faculty, such as the founder of the Plinian Society, Professor Jameson, and attend lectures at the Wernerian Society. Such digressions were clearly of great import to the young Darwin who noted that they 'had a good effect on me in stimulating my zeal and giving me new congenial acquaintances'.

Darwin's dislike of contemporary medical practice coupled with his obvious tropism for the natural world perhaps explains the relative absence of views on human health and disease in his voluminous writings. Perhaps also his lifelong struggle with ill health, for which there has never been any satisfactory understanding of what ailed him, might explain the lack of consideration of how evolution might shape disease susceptibility [3]. Finally, there is a strong sense of chosen social isolation that comes through his life—the Beagle voyage, life at Down House—indicative of a non-humanistic worldview. As an aside, he was, in this respect, quite unlike his grandfather Erasmus, one of the cofounders of the Lunatic Society, a group of industrial-age philosophers dedicated to the amelioration of the human lot. Returning to Charles Darwin, one might not expect discussion of human health in works such as Cirripedia (Darwin's tome on the humble barnacle) or, indeed, the *Origin of Species*, but consideration of disease is notably absent from the *Descent of Man*. Many opportunities present themselves in this book, but apart from the most cursory comment in the chapter on homological structures about the bidirectional nature of certain diseases between man and the lower animals, *Descent* is elsewhere silent on evolutionary considerations of health [4]. Nevertheless, it is the *Descent of Man* and the *Origin of Species* that provide the fundamental intellectual bedrock for understanding ultimate causation in human health and disease. In the following sections, we will briefly examine the importance of other central evolutionary figures to medicine, the rise of Darwinian medicine and its impact on cancer.

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post-Darwinian evolutionists

No discussion of Darwinian medicine can be complete without weaving in three giants of evolutionary biology responsible for the post-Darwinian synthesis of Mendelian genetics, systematics and Darwinian evolution as well as the development of the biological species problem. Our modern concept of evolution owes greatly to the seminal contributions made by all three—Dobzhansky, Mayr and Tinbergen.

The Ukranian Theodosius Dobzhansky, a pioneer of fruit fly genetics, was first to redefine evolution in terms of the new genetics as a 'change in the frequency of an allele within a gene pool' in his 1937 book *Genetics and the Origin of Species*.

Mayr was more critical of molecular evolutionary studies, particularly those Haldanian mathematical approaches, and, pertinent to our later discussions, rejected the idea of a gene-centred view of evolution. In a careful critique of Richard Dawkins's views, Mayr countered the single gene view of evolution by observing that 'a gene is never visible to natural selection, and in the genotype, it is always in the context with other genes, and the interaction with those other genes make a particular gene either more favourable or less favourable'. The species problem encountered by Darwin, how a single lineage could produce so many species, was also successfully dealt with by Ernst Mayr in *Systematics and the Origin of Species*. The third member of this illustrious triumvirate, Niko Tinbergen, revolutionised sociobiology and ethology. His work is particularly pertinent to Darwinian medicine. First, he was crystal clear, as were Huxley and Medawar in the '40s and '50s, that cultural evolution was distinct from genetic evolution; a factor that plays heavily when we come to consider the external risk factors associated with disease [5]. Second, he set out four questions that he believed should be asked of any animal behaviour, a framework with equal applicability in biomedicine. The four questions consider causation and development (ontogeny), the 'proximate' mechanisms, and evolution (phylogeny) and adaptation (function), which address 'ultimate' mechanisms (see Table 1).

As Mayr succinctly put it, 'no biological problem is solved until both the proximate and the evolutionary causation [ultimate] has been elucidated' [6]. Although the proximate approach has been hugely beneficial for the prevention and treatment of cancer, the Darwinian perspective can add new ways of thinking in terms of cancer susceptibility, patient treatment and the public understanding of cancer. As Mel Greaves, a leading evolutionary biologist and cancer expert notes, our current approach to cancer 'does not provide an adequate explanation for the prevalence of tumours and cancer in animal species or what seems to be the striking vulnerability of Homo sapiens' [7].

what is Darwinian medicine?

Darwinian medicine provides an explanatory framework that has real utility both for doctors and for patients in seeking to understand the why of health and disease. So often we struggle with various explanations to our patients about illness, and yet, in many cases, understanding why we are susceptible to certain diseases can provide a rational and exoteric framework to work

Table 1. Tinbergen's four questions

Proximate
Causation (mechanism): What stimuli elicit the response? How do molecular components function and what do the relations between the different levels look like? Most contemporary biomedical practice is concerned with this level.
Development (ontogeny): How do things change with age? Which developmental steps and which environmental factors function when/which role?
Ultimate
Evolution (phylogeny): How does the phenomenon compare with in related species, and how might this have arisen through the process of phylogeny? Why did these structural associations evolve in this manner and not otherwise?
Adaptation (function): How does the behaviour/phenomena impact on survival and reproduction?

within. Darwinian medicine also manifests itself in another way, as a provider of intellectual framework and methodological tools to drive biomedical research.

Over the past 20 years, techniques developed by evolutionary biologists to look at phylogenies have been successfully applied to pathogen evolution, e.g. human immunodeficiency virus and severe acute respiratory syndrome virus, as well as the emergence of antibiotic resistance. At the molecular level, mathematics arising from evolutionary biology has been instrumental for population genetics and the unravelling of the proximate mechanisms surrounding the human genome [8]. The same methodologies used in a variety of diseases to understand genome–environment interaction also owe their existence to evolutionary biology. At the practical level, Nesse and Stearn [8] have asked questions about why natural selection leads to disease vulnerability in the first place. For them, there are six reasons why we are vulnerable to disease:

Selection is slow
  1. Mismatch with the modern environment
  2. Pathogens co-evolve with hosts
What selection can do is limited
  3. Constraints on what selection can do
  4. Trade-offs
We misunderstand what selection shapes
  5. Selection maximises reproduction, not health
  6. Defences such as pain and fever are useful despite causing suffering

Evolution also helps us re-frame some of the most important questions for our species over the next 100 years, e.g. the interaction between health, disease and longevity. The question that arises is what exactly is the upper longevity barrier for *Homo sapiens*? Over the past 50 years, demographers have predicted time and again that the ceiling had been reached, and of course, on every occasion this has been surpassed as the 'mortality compression' effect took hold. Evolution helps us understand why this is happening, e.g. the longevity assurance theory related to capacity for DNA repair and the role of cultural transmission in the control of the environment [9].

Evolution tells us about the forces that have shaped the 'genetic architecture' of life. Tom Kirkwood has indicated that evolution has shaped what he terms a 'disposable soma', one in which there is a trade-off between our exposure to different background levels of mortality and the distribution of resources to either reproduction (if we live in a high-mortality background) or longevity (if we live in a low-mortality background) [10]. His theory indicates some sort of 'reserve', which, if we assume that recent hominid evolution had a 90% mortality by age 60, would give us another 30% on top as reserve. This indicates that we have evolved a genomic threshold. What does this mean for Darwinian medicine? It indicates that if we evolved in high-mortality environments, then selective advantages would have concentrated in early life (e.g. DNA repair). By definition, mutations that cause disease in post-reproductive lives are neutral. The exception to this is when post-reproductive longevity is somehow linked to pre-reproductive/intra-reproductive potential—the 'grandmother hypothesis'; this is the view that the menopause evolved to provide post-reproductive female carers for children and might indicate why we have sexual dimorphism in longevity that of females being far greater than of males (although this gap has now been substantially closed by cultural evolution) [11]. Furthermore, it is important not to forget that simply ascribing unhealthy longevity to external factors (diet, sedentary lifestyle) misses the point that humans have substantial genotypic variation making them more or less susceptible to a wide range of diseases depending on the environment [9].

Returning to Nesse and Stearn's six reasons for our vulnerability to disease, one of the most striking explanations is the mismatch problem. Hominid evolution has undergone three adaptive radiations as well as a variety of divergences and androgenic events within the context of altering habitat as a result of climatic changes. For 99% of hominid evolution we have just been another species, the evolutionary and behavioural ecology sets the costs and benefits of human evolution. Nevertheless, as cultural evolution began to dominate, humans drastically modified the ecosystem structure with cereal-based agriculture [12]. So rapid has been this last phase in human evolution (past 10 000 years) that mismatch has been inevitable. For example, from an evolutionary psychological point of view, we are 'made' to like salty, sweet, fatty foods. Moreover, we are now beginning to understand more about developmental mismatch where individuals adapted to one environment may be at risk when exposed to another when they are older. The work by Bateson et al. has done much to shed light on the relationship between adult health and nutritional *in utero* exposure and early development, as well as maternal exposure to glucocorticoids during fetogenesis [13].

molecular and cell biology of cancer: perspectives through the ideas of Darwin, Mayr and Lamarck

Remarkably, the concept of 'cellular Darwinism', in that Darwin's concept of the evolution of species might apply to cells, was widely and enthusiastically promulgated as early as the late 19th century. The views of Haeckel on survival advantage by mutation reached their logical conclusion with Wilhelm Roux who envisaged a struggle for survival between the body's cells, even down to the molecular level [14]. Nevertheless, these views fell mostly on deaf ears. This was the time of the great developmental biologists and as Virchow was clear, normal cells cooperate for the benefit of the whole organism. Evolution was competition and thus had no place in understanding normal or abnormal cells, which were seen almost entirely in the light of cooperation.

The question at the heart of the cellular and molecular biology of cancer is whether one can frame this in a Darwinistic manner. Bigold had argued forcibly that many of cancer's cellular features have no counterparts in Darwinian evolution described previously, citing the fact that tumour cell populations expand with few limits, that an 'inferior (less fit) cell grows excessively and dominates, and that the acceleration of cellular abnormalities coupled to the fact that these nearly always worsen have no equivalent in orthodox Darwinism' [15]. Although the latter point is valid, to equate cancer as 'inferior' and therefore not subject to Darwinian forces misses the point. The loss of specialised activity and increased growth rate are no less Darwinian than increasing specialisation. Nature is blind and there is no unidirectional a priori reason for increasing complexity. De-complexity, particularly if it leads to a 'survival advantage', i.e. increased growth rate, is equally Darwinian.

Ernst Mayr was clear on what criteria orthodox Darwinism should be judged against [16]:

1. The inconstancy of species (this is the theory of evolution)
2. The descent of all organisms from common ancestors
3. The gradualness of evolution
4. The multiplication of species
5. Natural selection, in particular the criteria to be considered as causes of species change, namely
   a. A fertile population so growth is exponential
   b. A population that is stable in size
   c. Limited resources available so that there is a struggle for existence between the individuals
   d. Normal minor variation between species undergoing change
   e. Hereditability of these variations
6. Increasing incidence of a particular variant in the population is associated with a survival advantage.

Cancer, in some way or the other, fulfils many, if not all, of these criteria. The view that cancers are heterogeneous aggregates of 'thousands of cells' dates to Virchow, in the mid-19th century, and cancers have been routinely treated as a single organism. Nevertheless, this view needs to be challenged in that we are now recognising that this heterogeneity is the ultimate expression of growth, random variation, differentiation and natural selection and that initial transformation may occur at single-cell level—the cancer stem cell. There is increasing evidence that a variety of cancers may arise through transformation of normal stem or progenitor cells. The properties of cancer stem cells could well fulfil the characteristics of orthodox Darwinism. Tumours are driven by a cellular component that retains stem cell properties, such as

stability, undifferentiation, long-term self-renewal, and capacity to replicate and undergo differentiation.

Why should we develop cancer at all? An obvious explanation is that it is an 'inevitable' outcome of a complex system subject to myriad internal and external stochastic events. Although stochastic forces certainly play a major role, it does not answer the question as to why, only in a sense does it give some explanatory power to the proximate mechanisms of carcinogenesis. In evolutionary terms, trade-off may play a major role. Natural selection favours early reproduction opportunities and traits that give advantage early in life and will tend to spread irrespective of the deleterious late-onset effects. Such trade-offs can be seen as a part of the intragenomic conflict between proto-oncogenes and tumour suppressor genes, which both have deep and crucial cladistic roles. Furthermore, there may be an even more fundamental trade-off. It is well recognised that viviparous animals have to suppress their immune systems to prevent the fetus from being rejected. Indirectly, this may also have lowered our ability to immunologically deal with aberrant 'self' cells, i.e. cancer cells [17]. The question behind this hypothesis is whether there really is a difference between viviparous and non-viviparous, e.g. mammalian and reptilian, rates of cancer? The answer is not clear-cut. Evidence from necropsy studies in captive animals does indicate that in reptiles the rates of cancer are one-eighth that of mammals (even this may be an overestimation as captivity rates are likely to be higher), but there are a whole host of other factors that may account for this [18]. Nevertheless, this provides an important mooring stake for an evolutionary perspective on the role of the immune system as a gatekeeper against cancer.

Although it is clear that the immune system has developed under the twin selective pressures of viruses/bacteria (Th1 mediated) and parasites (Th2 mediated), it is not clear what part, if any, the development of cancer has played. The question here is the relative importance of cancer immunosurveillance between childhood and around 40 years and whether the majority of cancer suppression is intrinsic and architectural (e.g. suppression of tumour angiogenesis). It is plausible that in hominid evolution, the greatest evolutionary pressure on the development of our immune system was external pathogenic threat—viruses, bacteria and parasites. Cancer suppression may be entirely a by-product of the gatekeeper functions associated with genomic integrity, e.g. DNA repair enzymes. This may go some way to explain why the immune system is so poor in tackling metastatic disease. It never evolved to do this.

Our susceptibility to cancer is often the result of trade-offs with fitness advantages, e.g., telomerases may provide stem cells with resilience and reproductive longevity but they also automatically provide immortality to emerging cancer clones. Likewise, a particular genotype for a woman who improves reproductive success may be detrimental later on by increasing her risk to certain cancers [7]. Indeed, we know that among all the primates, humans have one of the highest levels of body fat. In evolutionary terms, this enables females to reproduce quicker (inter-birth intervals of around 2 years) compared with other non-human primates, who, because of their low body fat, have much longer inter-birth intervals. Because of this more rapid rate of reproduction, and growth rate, there is a need for greater levels

of steroid hormones. This increased risk of higher exposure to pro-growth steroid hormones over sufficient time and at high enough levels can act as carcinogens resulting in an increased rate of steroid-induced cancers such as breast and prostate.

Beyond this thinking our understanding of adaptation must not be gene centred; rather, in light of Rupert Riedl's systems theory of evolution, recursive causality between the different players of the organism and its environment development sets the boundary conditions under which natural selection and variation take place [19]. Cancers spread along developmentally encoded boundaries. In this sense, the dynamic progression of cancer needs to be seen through an evolution–development perspective and not simply as a proliferation defect. As Vidal et al. [20] have described, cancer and development are two sides of the same coin, both shaped by evolutionary processes, affected by variations in complexity and plasticity, and operating within morphogenetic fields.

reframing cancer research in the light of evolution

There are numerous areas that evolution can help us re-think intellectual frameworks in cancer. One area is the drive for personalised cancer therapy. Much of the foundations for this are rooted in the belief that we can attain a certain clinically relevant degree of prognostication and prediction at the individual level. Nevertheless, if one considers cancer interacting with an individual geno-phenotype as a complex ecological interaction and consider the dynamic conditions under which this process occurs, then outcomes are indeterminate and hence unpredictable [21]. The reasons for this indeterminacy are, broadly speaking, fourfold. First, the randomness of an event with respect to the significance of the event, i.e. occurrence of a given cancer mutation, recombination and developmental homeostasis all make indeterminate contributions. Second, at higher levels of biological interaction, entities are unique. What we mean here is that each cancer in each patient is unique, and although one can have general valid predictive statements based on statistics, general laws have no place. Third, the almost unlimited structural and dynamical complexity makes complete description impossible. Systems biology in cancer in this sense provides us only with a 'probability cloud' of molecular and cellular interactions much in the same vein as Heisenberg's uncertainty principle. Finally, higher levels of integration give rise to the emergence of new properties. These emergent properties can neither be logical nor be predictable. Indeterminacy does not mean a lack of cause; it is simply unpredictable. This evolutionary thinking indicates that our ability at the individual level to predict outcomes and response to therapy is limited; this is cancer's event horizon.

Evolution also helps us ask fundamental questions about why cancer exists in the first place. Although it is clear that the more cells an organism has, the more the risk there comes, a point where a critical threshold is reached, a saturation rate of mutation beyond which in a relative sense the selective disadvantage does not increase. Error rates are magnified in eukaryotes and there is a 1% reduction in fitness per mutation; however, the power of random genetic drift is very powerful so

it is probably impossible to reduce error rates any further [22]. In hindsight, it is perhaps not surprising that we have not found any more 'high-penetrance' cancer genes as in evolutionary terms, large-effect mutations will be selected out of any given population. The more interesting question is whether certain cancer-predisposing genes are there because they give some fitness and/or reproductive advantage. Crespi and Summers are clear that the application of tools of ecology and evolutionary biology to cancer biology—phenotypic variation, selection, drift and inheritance—can provide highly novel insights into the patterns and processes of somatic evolution in cancer [23].

Darwin offers us a chance to practically enhance cancer treatment. Understanding disease and cancer in an evolutionary context provides a communication framework that can greatly aid public understanding of cancer and communication of causes and effects of this disease to patients and families. The use of evolutionary tools for studying cancer is another rich arena and new insights into gene culture co-evolution have the potential to bridge many of the dichotomous approaches we currently take to understanding the major public health issues in cancer such as obesity [24].

Richard Lewontin's description of geno–pheno 'spaces' has also been 'rediscovered' by the likes of Steppan et al. [25], who propose that complex emergent traits (e.g. cancer) integrate across the whole genome, hence explaining the failure of genome-wide association studies to fill the lacunae of 'missing hereditability'. This could allow us to measure the important dimensions of cancer and be able to think in terms of the cancer phenome. As phenotypic variation is co-structured, selection should leave signatures and as such metastasis, for instance, may perhaps be a measure of fitness. Should we consider using quantitative genetics (G matrix)—application(s) as a prognostic/predictive tool for cancer biology (with phenotypic matrix to map the adaptive landscape)? This can also be applied to our thinking of how tumour cells evolve resistance to treatment and how while increasing genetic instability might work in favour of a particular tumour in its adaptive landscape, incremental benefits of each 'mutation' can also lead to diminishing returns, i.e. the cancer becomes too unstable. Such a novel approach to the understanding of cancer could improve predictive modelling as well as influence how we schedule regimens for chemoradiotherapy. The key to advancing in these fields is better collaboration between evolutionary biologists and those engaged in cancer research. Extraordinary opportunities await such trans-disciplinary collaborations.

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